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First Identification of Compound Heterozygous *FKRP* Mutations in a Korean Patient with Limb-Girdle Muscular Dystrophy

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Dystroglycanopathies are a genetically and clinically heterogeneous group of muscular dystrophies that are characterized by reduced glycosylation of α-dystroglycan. Among 18 causative genes, the fukutin-related protein (*FKRP*; MIM 606596) gene is the most common cause in Caucasians.[1] However, *FKRP* mutations have rarely been found in the Asian population,[2] and have not been reported previously in Korea. Herein we report novel compound *FKRP* mutations in a patient with myopathy, which represents the first reported case in Korea.

A 43-year-old female (II-4) (Fig. 1A) was the fourth child of nonconsanguineous healthy Korean parents who achieved normal motor milestones after birth. She first noticed difficulty in climbing stairs at age 7 years, but muscle weakness did not progress. At the age of 23 years the patient perceived the progression of muscle weakness and was admitted to our institute. She displayed proximal weakness, especially in the pelvic girdle muscles. Mild winged scapulae and lordosis were also observed. No sensory deficits, joint contracture, tongue hypertrophy, or mental retardation were apparent. Her serum creatine kinase level was markedly elevated, at 2,439 IU/L (reference value: <185 IU/L). An electrophysiological study revealed a generalized myogenic process. No cardiac abnormality was observed. At the last examination, when she was 43 years old, she could walk with assistance.

The genetic cause of this patient's myopathy was evaluated by performing targeted sequencing of 69 myopathy-causative genes including *FKRP* (Supplementary Information, Supplementary Table 1, 2, and 3 in the online-only Data Supplement). DNA fragments in the target regions were enriched by solution-based hybridization capture, followed by sequencing with an Illumina Hiseq2000 platform. The sequencing data were analyzed using a standard pipeline. Variants were then filtered further based on the patient's phenotype. Compound heterozygous *FKRP* mutations of c.857G>C and c.1170_1171delGC were identified (Fig. 1B). The c.1170_1171delGC mutation has been reported previously in a Japanese patient with congenital muscular dystrophy.[2] However, the c.857G>C mutation was novel, and was not detected in 352 healthy controls, dbSNP138, or the 1000 Genomes Database (September 2014 release). *In silico* analysis using SIFT and PolyPhen2 predicted this mutation to be disease-causing. Genomic evolutionary rate profiling (GERP) indicated that the affected nucleotide is highly conserved (score=4.16), as became apparent upon inspection of the amino acid sequence in the altered region of the protein (Fig. 1C). Thus, the compound heterozygous *FKRP* mutations of c.1170_1171delGC and c.857G>C were determined to be the underlying cause of the myopathy in this patient.

FKRP mutations result in various clinical presentations from severe brain abnormality to mild limb-girdle muscular dystrophy.[1] This variability makes it difficult to diagnose *FKRP*-related muscular dystrophy based on clinical findings alone. Therefore, a step-by-step, clas-

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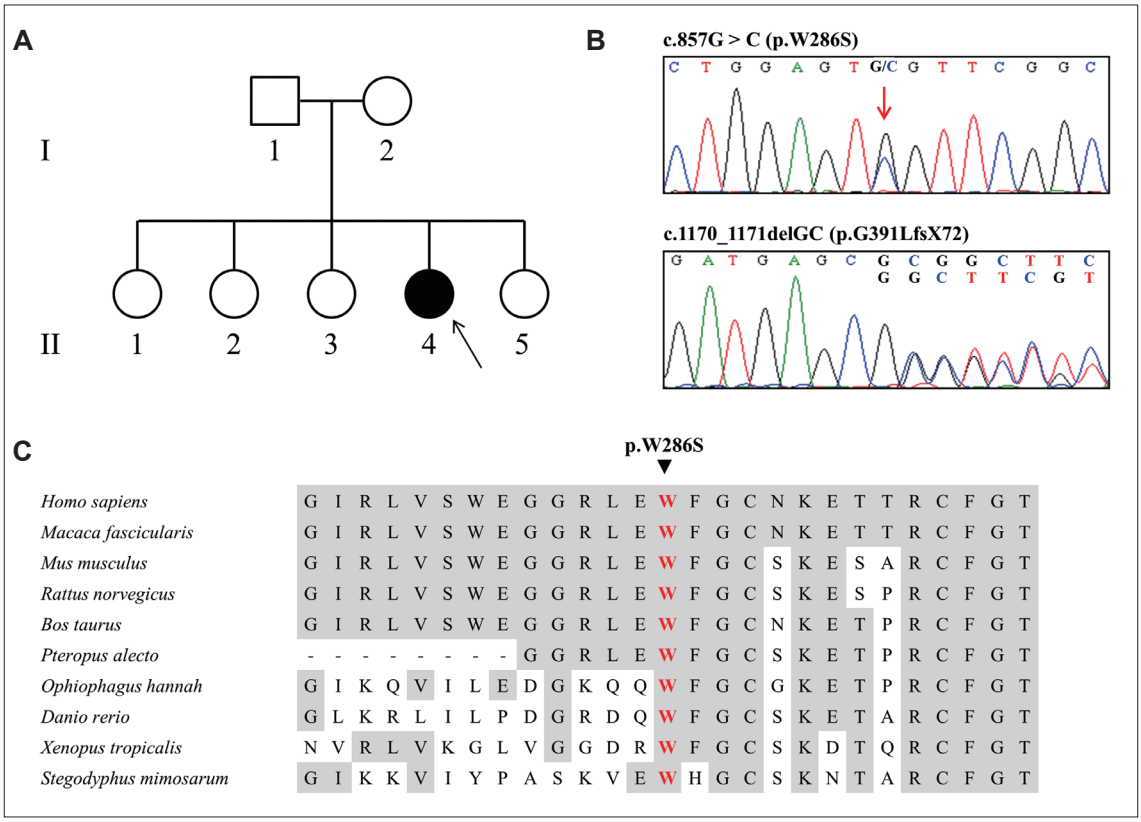

Fig. 1. Pedigree, sequencing chromatograms, and conservation profile of the patient. A: Pedigree of a Korean patient with compound heterozygous *FKRP* mutations. The filled symbol indicates the affected member; open symbols indicate unaffected members. B: Sequencing chromatograms of *FKRP* mutations c.857G>C and c.1170_1171delGC. C: Conservation analysis result of the c.857G>C mutation site. FKRP: fukutin-related protein.

sical approach with assessment of muscle pathology, muscle immunoanalysis, and mutational analysis is needed for the diagnosis of *FKRP*-related muscular dystrophy. The findings of a recent study in Taiwan that employed this approach suggested that *FKRP*-related muscular dystrophy is underdiagnosed, and not rare in the Asian population.[3] However, this classical approach often fails to identify the causative gene due to pathological variability and the limited power of muscle immunoanalysis. Advances in next-generation sequencing, including targeted sequencing, have enabled the rapid and cost-effective analysis of many causative genes in uncategorized muscular dystrophy.[4] In the present case, compound heterozygous *FKRP* mutations were identified using such next-generation sequencing.

In conclusion, novel compound heterozygous *FKRP* mutations were identified in a patient with limb-girdle muscular dystrophy; this is the first reported case in Korea.

Supplementary Materials

The online-only Data Supplement is available with this article at http://dx.doi.org/10.3988/jcn.2016.12.1.121.

Conflicts of Interest

The authors have no financial conflicts of interest.

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